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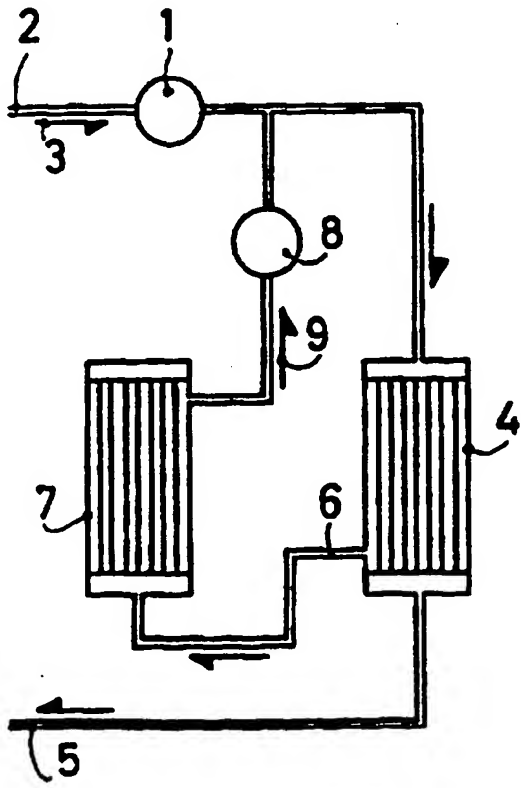
(54) Title: AN EXTRACORPOREAL BLOOD TREATMENT APPARATUS AND METHOD FOR REMOVAL OF FREE CIRCULATING INFECTIOUS AGENTS

(57) Abstract

In view of recently reported dynamics of HIV replication in vivo removal of the free HIV by continuous extracorporeal blood filtration may significantly and non-selectively reduce the total viral burden. A simple two-stage size separation circuit based on the available filtration technology and dialysis hardware for the treatment of acute renal failure should offer high single-pass elimination of the free virus suggesting a time constant of approx. 10 to 15 minutes for the systemic clearance. An acute treatment session of some ten days may tip the balance in favor of what now is known to be a massive and effective response of the immune system.



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An Extracorporeal Blood Treatment Apparatus and Method for Removal of Free Circulating Infectious Agents

Background of the invention

Recent reports (Wei,X. et al. Nature, 373,117-122,1995; Ho, D.,D, et al. Nature, 373, 123-126, 1995) on the *in vivo* turnover of human immuno-deficiency virus (HIV) have changed our perception of the dynamics of viral replication from the acute infection through the clinically latent period and to the eventual onset of the symptoms of acquired immunodeficiency syndrome (AIDS) (Coffin, J.,M. Science, 267, 483-489, 1995). This new data collected during perturbation transients caused by several different inhibitors of viral replication indicate turnover rates of the circulating HIV sub-population with the half-life of one to three days. These surprisingly high rates open a possibility of an acute attack on circulating HIV by means of extracorporeal blood treatment which may have significant impact on the course of infection. Reducing the viral burden by continuous clearing of the free HIV during a treatment session of circa ten days (which with the time constant of one day would lead to approx. 10^3 reduction in the amount of free virus) may shift the balance sufficiently to allow the immune system to clear out the rest. Since the strategies proposed here, in contrast to the available drug treatments, should in no way select for resistant sub-populations of HIV, the effectiveness of the immune response tuned to the total HIV population at the time of treatment should not be reduced. A theoretical possibility exists to further shorten the observed viral half-lives by stimulating infected cells to express HIV. On-line capacity for HIV clearance should be sufficient to deal with the increased HIV production once the initial burden has been reduced -- if means of such stimulation were available they should be used in the later part of a given treatment session.

The simplest approach, and the preferred embodiment calls for elimination of the circulating HIV by continuous on-line size separation in a two-stage extracorporeal blood filter shown on Figure 1. There are no volumetric changes of the blood in this closed system -- once the equilibrium is reached between the solutes in the fluid in the secondary circuit and in the blood, no effects other

than entrapment of the HIV particles and possibly some cellular debris should be exerted on the patients blood. Typical blood flow rates, which can be routinely maintained for several days by the use of state-of-the-art dialysis equipment on acute renal failure patients, are 0.2 to 0.5 l/min. The secondary circuit could be pumped at several times this rate, say at 2 l/min. This would suggest up to 80% single pass removal of HIV. Two serially connected stages would practically eliminate free HIV particles from the blood in the return line. This would result in an approximately 10 to 15 min time-constant for elimination of the free HIV from the patient's vascular and lymphatic system. While details of HIV infection dynamics in vivo are not precisely known, this time constant appears short enough to allow for a major interruption of the cell-to-cell viral transfer.

Another, somewhat more involved approach, would use combined size and affinity separation schematically shown on Figure 2. The filtrate of the first filter is now mixed with a medium carrying gel beads with immobilized CD4 receptor. The reactor transit time is made long enough (by its volume) to allow binding of HIV particles to the gel beads. The beads are confined to the secondary circulation by the second filter which now can have the same or larger pore size than the first filter. This would basically eliminate retention of any normal components of the blood in the extracorporeal circuit. Use of a packed gel column instead of the second filter and the reactor could be considered, but may be complicated by plugging of the column. Conceivable, but much more involved, would be HIV removal by appropriate CD4-expressing cells in the secondary circuit as shown on Figure 3.

It is unreasonable to speculate on chances of eliminating HIV from an infected individual - total elimination, if possible at all, would have to come through the response of a fully competent immune system. The argument for this approach is that the balance in the fight the immune system is mounting throughout the protracted course of the infection might be decisively tipped against the virus

by one or several such interventions. Application of this treatment modality at the earliest time possible reduces the chances of a broad spread infection. Some of the currently available anti viral drugs are more effective if used against the residual virus population at the end of the acute extracorporeal blood treatment (in view of possibly reduced burden of drug-resistant variants). With some interleukins, specifically IL-2 and IL-12, interferons, specifically interferon-gamma, and tumor growth factors, used to enforce the expression of HIV in infected cells the chances of virus elimination should certainly improve. With the virus half-life reduced to for example 1/2 of a day, a ten day session leads to a 10^6 fold reduction in the number of circulating virus. While the use of such means, without concurrent possibility to efficiently eliminate free virus, would certainly lead to worsening of the situation, they could be safely deployed with the patient on-line of an extracorporeal filter proposed here. Given the obvious possibility of repeated treatment sessions, even a temporary relief of perhaps several months in duration may be worth the effort.

List of Figures

1. A simple two-stage size separation filter

2. A two stage combined size separation / affinity filter

3. A two stage combined size separation / cellular uptake filter

4. A serial double filter

5. A single stage affinity filter

6. A venturi-type blood pump

Detailed description

Figure 1 shows an arterial-venous extracorporeal circuit with a two-stage size separation. The blood is pumped by the blood pump, 1, from the arterial line, 2, at the flow rate, 3, through the first filter, 4. The first filter is preferably of hollow fiber type with the pore size of 0.1 to 2 micrometers, preferably 0.2 to 0.5 micrometers. Hollow fiber-type filter with the 0.2 micrometers pore size is commercially available. This should allow for a relatively free passage of HIV particles which are 0.1 micrometers in diameter. Blood cells are retained by the first filter and pass directly into the venous line, 5. The filtrate, 6, of the first filter carrying viral particles is passed through the second filter, 7, with the pore size in the range of 0.02 to 0.08 micrometers, preferably of 0.04 to 0.06 micrometers. A filter with 0.05 micrometers is commercially available. This will trap most of the virus and allow for basically unrestricted passage of most macromolecular species found in the blood, which are thus mixed back into the blood stream. The cutoff of the filter with the pore size of 0.05 micrometers is considered approx. equivalent to the cutoff of 10^6 Daltons. The second pump, 8, moves the secondary circuit fluid in the closed circulation compensating for the pressure drops caused by the flow, 9, across both filtering membranes.

Figure 2 shows an extracorporeal blood filter with combined size / affinity separation. The filtrate, 11, from the first filter 10 is now mixed with the retentate, 12, of the second filter, 13, which contains gel beads, 14, with the immobilized CD4 receptor. The mixture is passed through the reactor, 15, allowing gel beads to collect HIV particles. The third pump, 16, maintains circulation, 17, in the tertiary circuit. The filtrate, 18, of the second filter, 13, is pumped by the second pump, 19, and mixed with the blood stream, 20, pumped by the first pump, 21, from the arterial line 22. Blood is returned to the patient via venous line 23.

Figure 3 shows the combined size separation / cellular uptake filter. Configuration is identical to that of Figure 2 except for the cell support system depicted schematically as 30. Gel beads are here replaced by a suitable cell line, preferably a hybridoma 29 expressing the CD4 receptor.

In any of the filters described above, the removal (filtration) efficiency is basically determined by the ratio of blood flow to the secondary circuit flow. For example, if, in referring to Figure 1, the blood flow rate, 3, is four times lower than the secondary circuit flow rate, 9, the expected removal efficiency is 80%. This assuming perfect filtration of both filters, i.e. no retention in the first filter and 100% retention in the second filter. Thus the best way to maximize the removal efficiency is to increase the ratio of the flow rates in the secondary and the primary circuits. Once this has been done a further improvement is possible by serially connecting two filtration stages as shown on Figure 4. If each stage has the flow ratio of four, total removal efficiency is now 96%. Note that only one blood pump, 31, is used for both primary filters, 32 and 33. There are two secondary pumps, 34 and 35, for the secondary filters, 36 and 37.

Figure 5 shows a single stage affinity filter, whereby the blood is pumped by the pump 38 through the filter 39 and back into the patient. This simple configuration calls for special technologies, however, in order to safely immobilize the receptor onto the blood contacting surfaces. In case of HIV this would be preferably CD4. The filter needs a very large area in order to achieve high efficiency of removal, but the advantage is that a single blood line connected between an artery and a vein could make the use of pump unnecessary. Reducing damage to blood cells is an important issue for a prolonged treatment.

Figure 6 shows an alternative solution to reducing blood cell damage. Blood pump is now of the venturi type, i.e. there is no mechanical damage being inflicted on the blood cells as is the case

in conventional peristaltic pumps. Venturi pump 40 is powered by the flow of the secondary circuit pump 41.

In the description of the preferred embodiments given above, preference was given to describing application to removal of free HIV particles from the blood of an infected patient. It is understood that the same invention can be applied to other circulating infectious agents of either viral or bacterial origin. One particular example where this invention may find good use is that of the septic shock caused by the bacterial invasion through the compromised intestinal barrier. There is no efficient treatment for this condition and most patients die within a short time. The difference now is the size of the infectious agent, typically 0.5 to 1 micrometers, i.e. some ten times larger than most viruses. Thus the first filter, which should allow for free passage of the bacteria should have pore size in the range of 1 to 5 micrometers (which will still retain blood cells), preferably 2 to 3 micrometers. The second filter should retain the bacteria, so the range should be 0.1 to 0.5 micrometers. Typical sterilization filters used in the laboratory practice have either 0.22 or 0.45 micrometers pore size. The largest pore size available in the hollow fiber-type filters is 0.2 micrometers. This would be the prefered filter for the second stage separation.

Method of treatment according to the invention calls for connecting the patient to the extracorporeal circuit, which in a typical situation is to be done in a clinical setting. While the patient's freedom of movement is significantly restricted, he is not necessarily confined to bed for the full duration of a single session. Duration of the session depends on the conditions of viral turnover. In some HIV infected patients the half-life of virus has been measured as one day only. A ten day session should lead to a thousand-fold reduction in the number of free virus, should no other effects help to speed up the removal, notably the response of the immune system. It is possible to push the expression of virus in the infected cells by systemic administration of molecular signals known to activate CD4 lymphocytes. These include certain

interleukins (IL-2 and IL-12 particularly), interferons (gamma) and tumor growth factors. Reducing the virus half-life to for example 1/2 day could lead to a million-fold reduction of the viral burden in a ten day session.

Claims:

1. Extracorporeal blood treatment apparatus comprising: (a) separation means (4, 7; 10, 13, 14; 29; 32, 36, 33, 37; 39) for substantially continuous, on-line removal of infectious agents from the rest of the patient's blood; (b) circulation means (1, 2, 5, 8; 21, 22, 23, 16, 19; 31, 34, 35; 38; 40, 41) for moving said patient's blood from the patient through said separation means and moving said rest of said patient's blood back into said patient.

2. Blood treatment apparatus according to claim 1 whereby said means for separation and removal of infectious agents comprise: (a) first separation means (4; 10; 32, 33) for separating said infectious agents suspended in a fraction of a mixture of a suspending medium admixed to the blood prior to entry into said first separation means and the blood plasma from the blood cells suspended in the rest of the suspending mixture; (b) second separation means (7; 13, 14, 15; 29; 36, 37) for separating said infectious agents from said fraction of said suspending mixture.

3. Blood treatment apparatus according to claim 2 whereby said first separation means for removal of infectious agents from the blood comprise a filter, whereby said filter has an inner and an outer compartment separated by a filter membrane, preferably of the hollow fiber type, which allows substantially free passage of said infectious agents across said filter membrane into the first filtrate (6; 11) collected in and removed from said outer compartment and which confines the blood cells to said inner compartment from which said blood cells are removed with the first retentate.

4. Blood treatment apparatus according to claims 2 or 3 whereby said second separation means for removal of infectious agents from said filtrate of said first separation means comprise a filter, preferably of the hollow fiber type, which retains said infectious agents and allows substantially free passage of said suspending

mixture into the second filtrate (9), which is then admixed back into the stream of said blood entering the first separation means.

5. Blood treatment apparatus according to claims 2 or 3 whereby said second separation means for removal of infectious agents from said filtrate of said first separation means comprise an affinity filter (13,14,15) which retains said infectious agents by specific, receptor-mediated adsorption and allows substantially free passage of said suspending mixture into the second filtrate (18), which is then admixed back into the stream of said blood entering the first separation means.

6. Blood treatment apparatus according to claim 3 whereby pore size of said filter of said first separation means is in the range of 0.1 to 2 micrometers, preferably in the range of 0.2 to 0.5 micrometers, which is suitable for separation of infectious agents of viral origin.

7. Blood treatment apparatus according to claim 4 whereby pore size of said filter of said second separation means is in the range of 0.02 to .08 micrometers, preferably 0.04 to 0.06 micrometers, which is suitable for separation of infectious agents of viral origin.

8. Blood treatment apparatus according to claim 3 whereby pore size of said filter of said first separation means is in the range of 1 to 5 micrometers, preferably in the range of 2 to 3 micrometers, which is suitable for separation of infectious agents of bacterial origin.

9. Blood treatment apparatus according to claim 4 whereby pore size of said filter of said second separation means is in the range of 0.1 to .5 micrometers, preferably 0.15 to 0.3 micrometers, which is suitable for separation of infectious agents of bacterial origin.

10. Blood treatment apparatus according to claim 5 whereby said affinity filter contains gel beads-immobilized CD4 receptor (14).

11. Blood treatment apparatus according to claim 2 whereby said circulation means comprise: (a) a blood pump (1; 21; 31) moving said blood from said patient through said first separation means and back into said patient; (b) a secondary circulation pump (8; 19; 34, 35) moving the filtrate from said first separation means through said second separation means; (c) a set of fluid lines for connecting said pumps and said separation means so that the outflows from said pumps are mixed prior to entering said first separation means.

12. Blood treatment apparatus according to claim 2 whereby said circulation means comprise: (a) a blood pump moving said blood from said patient through said first separation means and back into said patient; (b) a secondary circulation pump moving the filtrate from said first separation means through said second separation means; (c) a set of fluid lines for connecting said pumps and said separation means so that the outflows from said pumps are mixed prior to entering said first separation means, whereby said blood pump is a venturi-type pump (40) powered by the flow of said secondary circulation pump (41).

13. Method of extracorporeal on-line treatment of patient's blood containing infectious agents by feeding said patient's blood into an external circuit, separating said infectious agents from said blood in said external circuit by separation means and returning the rest of said blood to the patient.

14. Method of extracorporeal on-line treatment of patient's blood according to claim 13, whereby said infectious agents are of viral origin.

15. Method of extracorporeal on-line treatment of patient's blood according to claim 13, whereby said infectious agents are of bacterial origin.

16. Method of extracorporeal on-line treatment of patient's blood according to claim 13, whereby said infectious agents are from the family of Human Immunodeficiency Viruses (HIV's).

17. Method of extracorporeal on-line treatment of patient's blood according to claim 13, whereby said infectious agents are from the family of hepatitis-causing viruses.

18. Method of extracorporeal on-line treatment of patient's blood according to claim 13, complemented by the systemic administration to the patient of interleukins, particularly of IL-2, or of IL-12.

19. Method of extracorporeal on-line treatment of patient's blood according to claim 13, complemented by the systemic administration of interferons, particularly of the interferon-gamma.

20. Method of extracorporeal on-line treatment of patient's blood according to claim 13, complemented by the systemic administration of tumor growth factors.

21. Method of extracorporeal on-line treatment of patient's blood according to claim 13, whereby a single session of treatment is at least one day long, and preferably 7 to 28 days.

22. Method of extracorporeal on-line treatment of patient's blood according to claim 13, whereby the blood flow through the external circuit is in the range of 0.1 to 0.6 liters/minute.

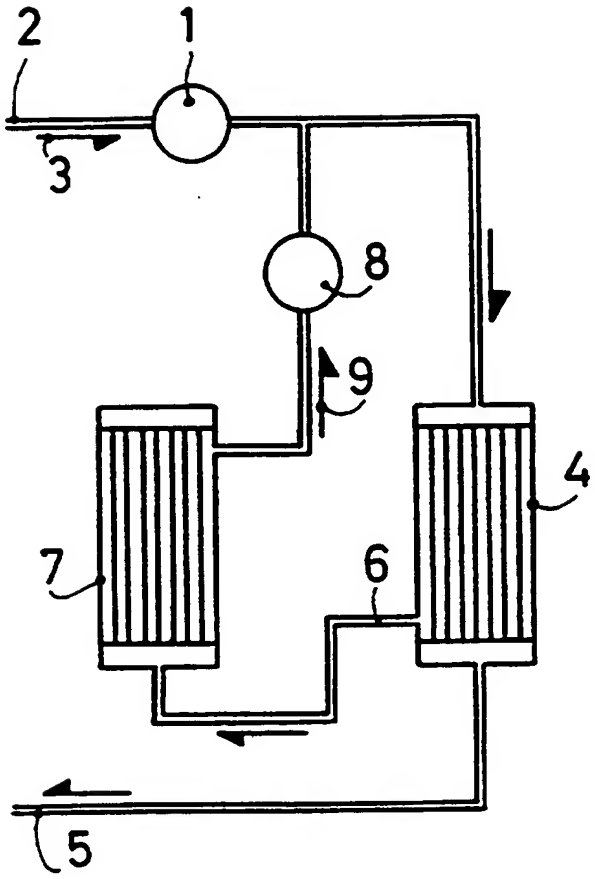

FIGURE 1

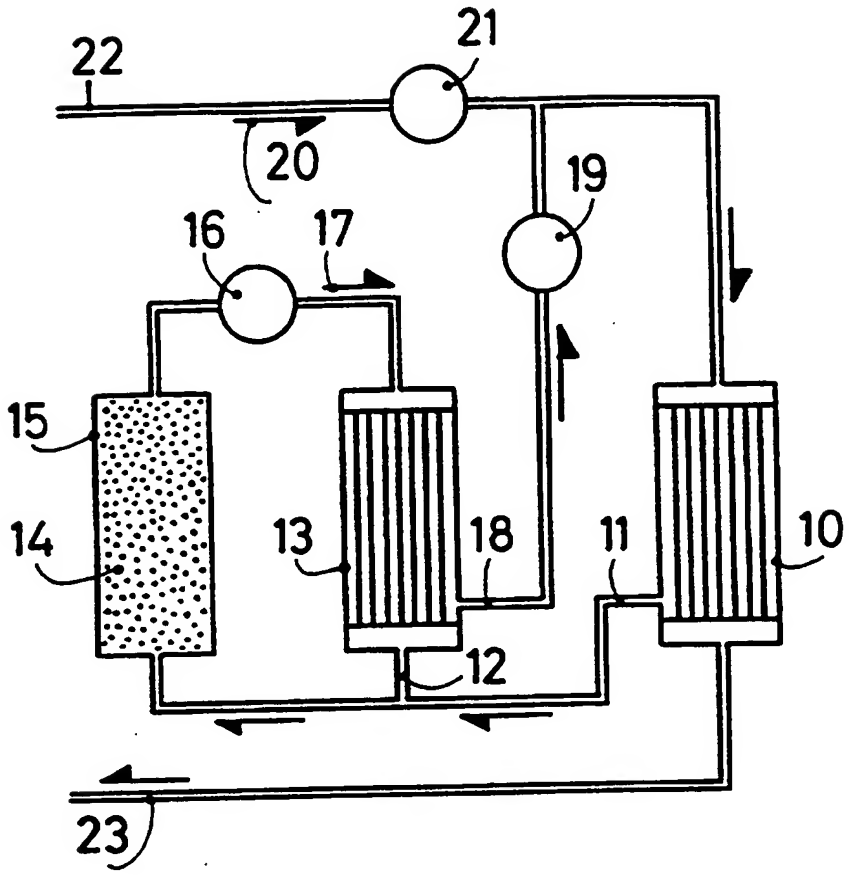

FIGURE 2

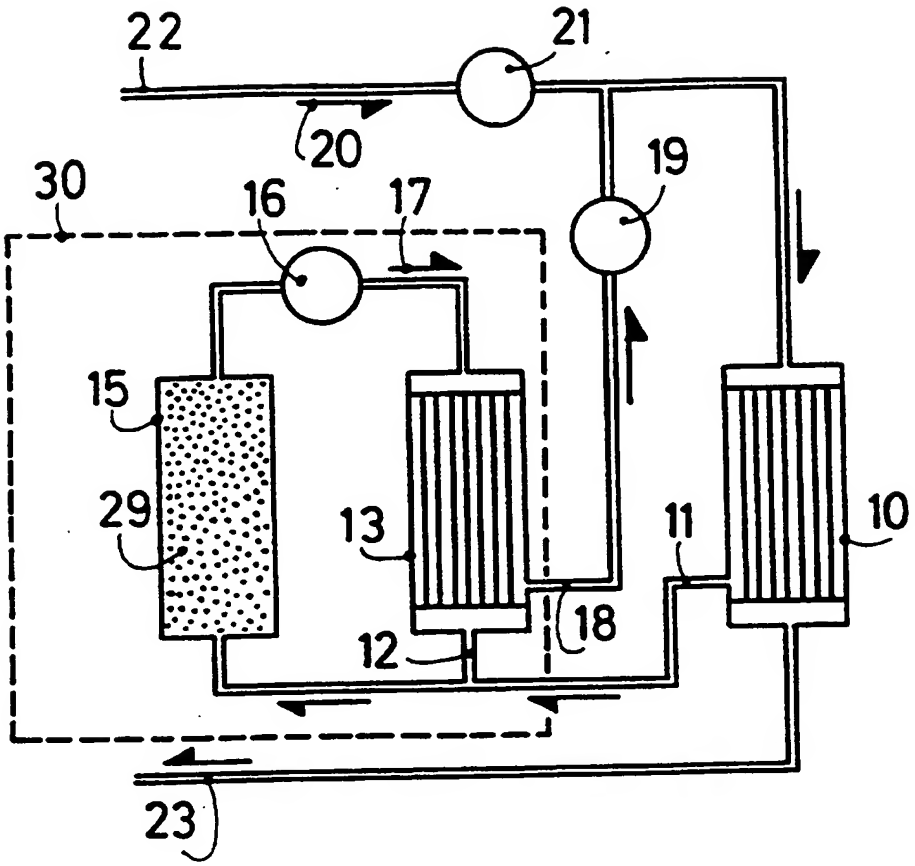

FIGURE 3

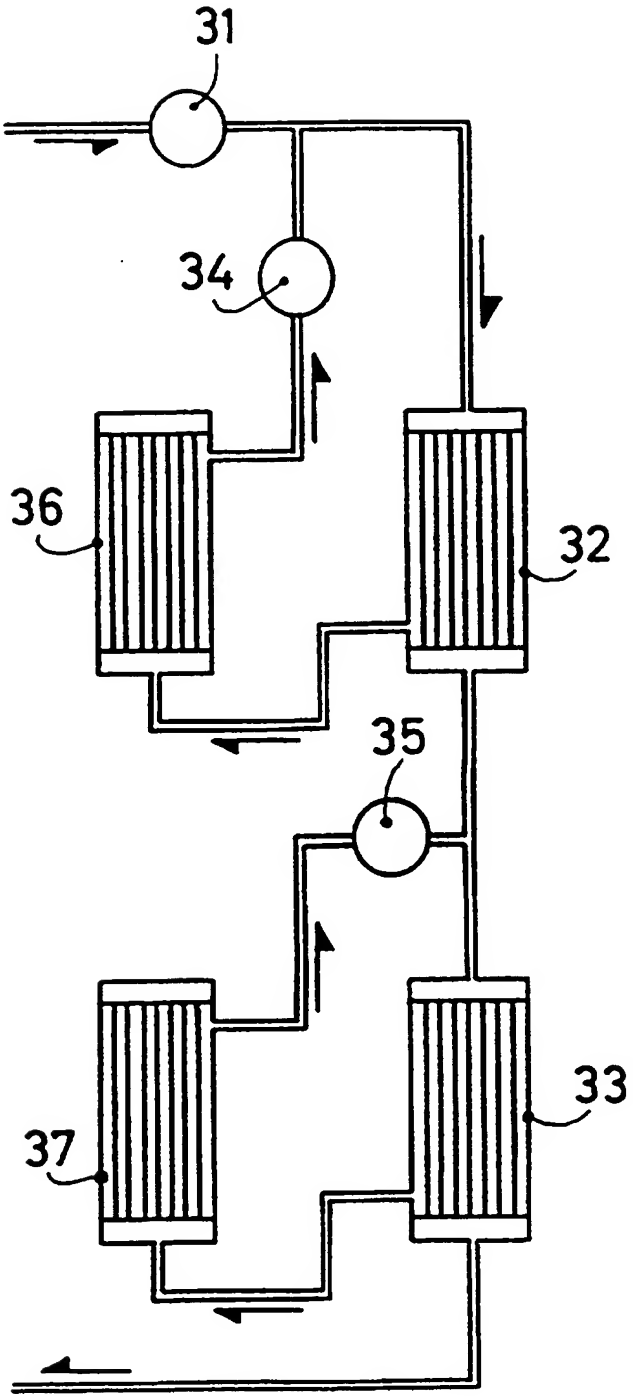

FIGURE 4

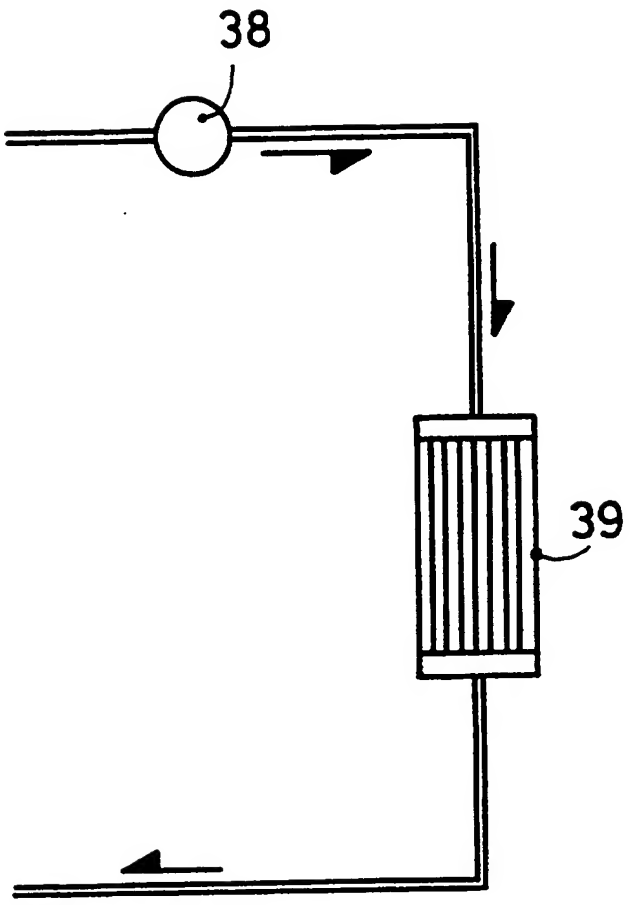

FIGURE 5

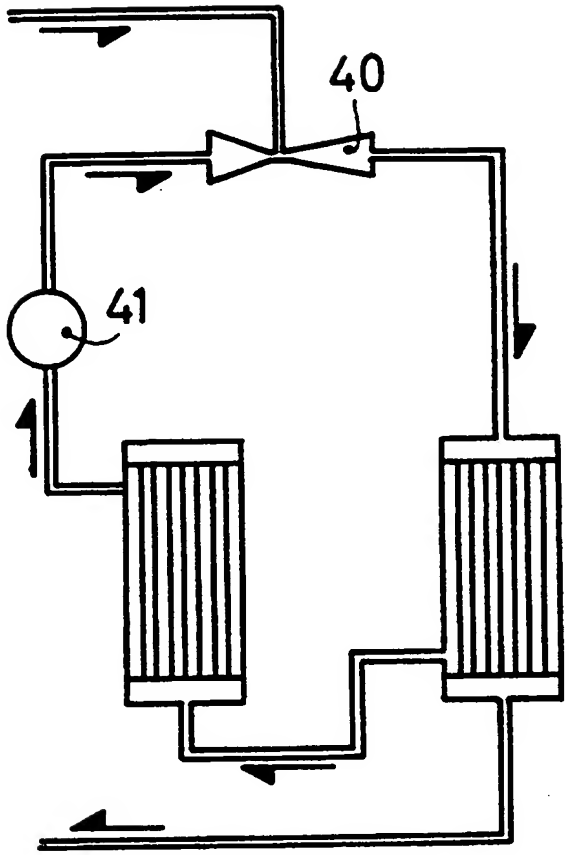

FIGURE 6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/00929

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 232 884 (MILLIPORE CORP.) 19 August 1987 see page 5, line 46 - page 6, line 29	1-3,6
A	---	4
X	EP,A,0 038 203 (KURARAY CO LTD) 21 October 1981 see page 1, line 8 - line 10 see page 2, line 35 - page 3, line 6 see page 3, line 22 - page 4, line 1 see page 7, line 13 - line 17 see figures	1-3,5,6
Y	---	4,7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 December 1995	07. 12. 95

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Int. .onal Application No
PCT/EP 95/00929

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR,A,2 325 390 (ASAHI KASEI KOGYO) 22 April 1977 see page 6, line 18 - line 32 see page 7, line 35 - page 8, line 5 see figure 2	1-3,5,6, 11
Y	---	4
X	WO,A,95 04560 (AO FORSCHUNGSINSTITUT) 16 February 1995 see claims see figure 16	1-5,11

X	BIOMEDIZINISCHE TECHNIK, vol. 28, no. 6, June 1983 BERLIN, pages 137-144, H.VON BAYER 'Ein neues Verfahren zur Durchfürung der Kaskadenplasmapherese' see page 138, column 1, line 20 - line 35 see page 144, column 1, line 18 - line 35 see figure 1	1-3
Y	---	7
X	MALCHESKY P S ET AL 'ARE SELECTIVE MACROMOLECULE REMOVAL PLASMAPHERESIS SYSTEMS USEFUL FOR AUTOIMMUNE DISEASES OR HYPERLIPIDEMIA?' 1 October 1993 , ASAIO JOURNAL, VOL. 39, NR. 4, PAGE(S) 868 - 872 see the whole document	1-3

A	DATABASE WPI Section Ch, Week 9212 Derwent Publications Ltd., London, GB; Class A96, AN 92-093179 & JP,A,04 036 656 (ASAHI MEDICAL KK) , 6 February 1992 see abstract	10

A	DATABASE WPI Section Ch, Week 9530 Derwent Publications Ltd., London, GB; Class A97, AN 95-227588 & JP,A,07 136 505 (TERUMO CORP) , 30 May 1995 see abstract	10

1

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 95/00929

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13- 22
because they relate to subject matter not required to be searched by this Authority, namely:
PCT Rule 39.1(iv)

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 95/00929

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		JP-A-	56145859	12-11-81
		JP-B-	63027023	01-06-88
		JP-A-	56145860	12-11-81
		CA-A-	1151044	02-08-83
		US-A-	4350594	21-09-82
FR-A-2325390	22-04-77	JP-C-	1056291	23-07-81
		JP-A-	52118895	05-10-77
		JP-B-	55009227	08-03-80
		JP-C-	1163128	10-08-83
		JP-A-	52039997	28-03-77
		JP-B-	55022107	14-06-80
		DE-A-	2642535	07-04-77
		GB-A-	1558370	28-12-79
		US-A-	4518497	21-05-85
		US-A-	4243532	06-01-81
WO-A-9504560	16-02-95	AU-B-	7498994	28-02-95
		EP-A-	0671958	20-09-95